Safety Data Sheet

4-Ipomeanol

Division of Safety
National Institutes
of Health

WARNING!

THIS COMPOUND IS ACUTELY TOXIC. IT IS READILY ABSORBED THROUGH THE INTESTINAL TRACT. IT MAY CAUSE SEVERE DAMAGE TO THE LUNG. AVOID FORMATION AND BREATHING OF AEROSOLS.

LABORATORY OPERATIONS SHOULD BE CONDUCTED IN A FUME HOOD, GLOVE BOX, OR VENTILATED CABINET.

AVOID SKIN CONTACT: IF EXPOSED, WASH WITH SOAP AND COLD WATER. AVOID WASHING WITH SOLVENTS AND EXPOSURE TO UV LIGHT. AVOID RUBBING OF SKIN OR INCREASING ITS TEMPERATURE.

FOR EYE EXPOSURE, IRRIGATE IMMEDIATELY WITH LARGE AMOUNTS OF WATER. FOR INGESTION, INDUCE VOMITING. DRINK MILK OR WATER. REFER FOR GASTRIC LAVAGE. FOR INHALATION, REMOVE VICTIM PROMPTLY TO CLEAN AIR. ADMINISTER RESCUE BREATHING IF NECESSARY. REFER TO PHYSICIAN.

IN CASE OF LABORATORY SPILL, WEAR PROTECTIVE CLOTHING DURING CLEANUP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS. USE METHANOL TO DISSOLVE COMPOUND. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

A. Background

4-Ipomeanol (4-IP) is the main toxic compound formed as the result of microbial infection in sweet potatoes (Ipomoea batatas). Several other more or less closely related compounds with qualitatively similar but quantitatively varying toxic properties are also found as the result of infestation. It is probably (no literature statement) a white crystalline compound, soluble in propylene glycol and methanol. Its chief toxic action is to produce pulmonary edema and congestion and severe respiratory distress leading to death in several animal species, with a less pronounced action on the kidney

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and/or lung. These symptoms are the result of activation in Clara and alveolar type II cells, followed by irreversible binding to macromolecular cell constituents.

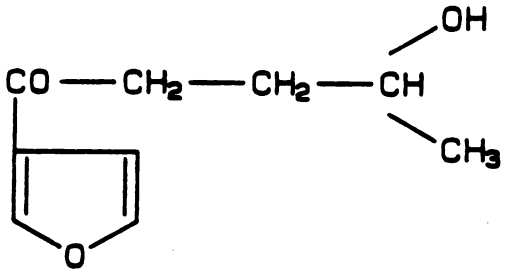
The chemical and toxicological properties of 4-IP and related compounds have been reviewed (Boyd et al., 1973; Wilson, 1973; Boyd 1980).

3. Chemical and Physical Data

1. Chemical Abstract Nos.: 32954-58-8 (usual); 55659-41-1 (apparently a duplicate number); 36878-93-0 (for the racemic form).

2. Synonyms: 1-Pentanone, 1-(3-furyl)-4-hydroxy-;[A] 1-pentanone, 1-(3-furanyl)-4-hydroxy-.[B]

3. Chemical structure and molecular weight:



$C_9H_{12}O_3$; 168

Related (toxic) compounds

a. 1-ipomeanol;

b. ipomeanine [1-(3-furanyl)-1,4-pentanedione];

c. 1,4-ipomeadiol [1-(3-furanyl)-1,4-pentanediol;

d. See Wilson et al. (1970) for structures and descriptions o ipomeamarone and ipomeamaronol.

4. Density: No data.

5. Optical rotation: $[\alpha]_D = +7.86 \pm 1.45$.

6. Absorption spectroscopy: Ultraviolet absorption maxima (ε) are 211(6,100), 251(2,970) in methanol. Infrared, NMR, and mass spectral data have been published (Boyd et al., 1973).

[A] Chemical Abstracts name, used for listings in 8th Decennial Index.
[B] Chemical Abstracts name, used for listings in 9th Decennial Index and subsequently.

7. Volatility: No data.

8. Solubility: For parenteral injection, 4-IP is usually dissolved in propylene glycol and this stock solution is diluted in water to yield a 25% propylene glycol solution. 4-IP is also soluble in methanol and cyclohexane since spectral data in these solvents have been published.

9. Description: No literature statement but may be assumed to be a white crystalline compound.

0. Boiling point: No data; melting point: No data.

1. Stability: Appears to be very heat stable since normal baking or boiling does not remove 4-IP from infested sweet potatoes (Wilson et al., 1970). Solutions in 25% propylene glycol are stable in the dark at 4°C for at least 3-4 weeks (Boyd and Burka, 1978).

2. Chemical reactivity: There are no literature data on this but it may be assumed that 4-IP is subject to oxidation and reduction at the 1- and 4- positions since such derivatives are formed at least biologically (see B3). The furan ring is probably subject to hydroxylation (as it is in aflatoxins) and it has been speculated that the "active metabolite" or its precursor may be an epoxide (Boyd et al., 1975). The 4-glucuronide of 4-IP is a major urinary excretion product. Strong oxidizing agents probably destroy the furan ring which is essential for toxic activity.

3. Flashpoint: No data.

4. Autoignition temperature: No data.

5. Explosive limits in air: No data.

ire, Explosion, and Reactivity Hazard Data

1. 4-IP does not require special fire-fighting procedures or equipment and does not present unusual fire and explosion hazards.

2. The presence of strong alkali and/or oxidants probably contributes to the instability of 4-IP.

3. No incompatibilities are known.

4. 4-IP does not require non-spark equipment.

Operational Procedures

The NIH Guidelines for the Laboratory Use of Chemical Carcinogens describe operational practices to be followed when potentially carcinogenic chemicals are used in NIH laboratories. The NIH Guidelines should be consulted to identify the proper use conditions required and specific controls to be implemented during normal and complex operations or manipulations involving 4-IP.

It should be emphasized that this data sheet and the NIH Guidelines are intended as starting points for the implementation of good laboratory practices when using this compound. The practices and procedures described in the following sections pertain to the National Institutes of Health and may not be universally applicable to other institutions. Administrators and/or researchers at other institutions should modify the following items as needed to reflect their individual management system and current occupational and environmental regulations.

1. Chemical inactivation: No validated method reported.

2. Decontamination: Turn off equipment that could be affected by 4-IP or the materials used for cleanup. If there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 116) for assistance. Wipe off surfaces with methanol, then wash with copious quantities of water. Glassware should be rinsed (in a hood) with methanol, followed by soap and water. Animal cages should be washed with water.

3. Disposal: No waste streams containing 4-IP shall be disposed of in sinks or general refuse. Surplus 4-IP or chemical waste streams contaminated with 4-IP shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Nonchemical waste (e.g., animal carcasses and bedding) containing 4-IP shall be handled and packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., tissue cultures) containing 4-IP shall be packaged for incineration, as above. Burnable waste (e.g., absorbent bench top liners) minimally contaminated with 4-IP shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g., associated with spill cleanup) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing 4-IP shall be handled in accordance with the NIH radioactive waste disposal system.

4. Storage: Store solid 4-IP and its solutions in dark-colored, tightly closed containers, preferably under refrigeration. Avoid exposure to light and moisture. Store working quantities of 4-IP and its solutions in an explosion-safe refrigerator in the work area.

Monitoring and Measurement Procedures Including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis

There are no published procedures for the analysis of 4-IP. All metabolic studies have been carried out using isotopically labeled 4-IP.

Biological Effects (Animal and Human)

1. Absorption: 4-IP appears to be readily absorbed from the gastrointestinal tract since it is as toxic orally as parenterally.

2. Distribution and pharmacokinetics: After intraperitoneal administration to rats of 4-IP, ^{14}C-labeled in the side chain, approximately half of the radioactivity is found in the urine within 2 hours, with only traces in feces and expired air. The highest tissue concentration is found in the lung, with smaller amounts in the liver, kidney, and gastrointestinal tract. In these tissues the concentration is maximal within one hour, followed by a decline to a plateau (Boyd *et al.*, 1975; Statham *et al.*, 1982)

3. Metabolism and excretion: *In vivo* and *in vitro* studies of the metabolism of 4-IP have concluded that 4-IP is activated to an alkylating agent by an oxidative metabolism involving cytochrome P-450-dependent mixed function oxidases, NADPH, and oxygen (Boyd *et al.*, 1978; Wolf *et al.*, 1982). The metabolite forms derivatives with tissue glutathione, and there appears to be an inverse relationship between tissue glutathione level, and both toxicity and covalent binding of 4-IP to microsomal macromolecules. For instance, pretreatment of animals with piperonyl butoxide (which inhibits metabolic activation) or with cysteine or cysteamine prevent glutathione depletion and pulmonary toxicity in rats, while pretreatment with diethyl maleate (which depletes tissue glutathione) has the opposite effect (Boyd *et al.*, 1982). The site of this metabolic activation varies with animal species; in all mammalian species studied including man (Falzon *et al.*, 1986) it takes place mainly in the Clara cells and to a lesser extent in alveolar type II cells, while several birds which lack these pulmonary cells and are low in the pulmonary cytochrome oxidase activating activity the same reaction is found in the liver instead (Buckpitt *et al.*, 1982). Excretion of radioactivity due to labeled 4-IP is largely in the form of the 4-glucuronide (Statham *et al.*, 1982); glutathione conjugates, which on the basis of the above evidence might be expected to constitute other excretory products, have been identified *in vitro* (Buckpitt and Boyd,1980) but not *in vivo*.

4. Toxic effects: The intraperitoneal LD50 is in the range of 10-60 mg/kg in most mammalian species (mouse, rat, guinea pig, rabbit); the hamster appears to be somewhat more tolerant

(150 mg/kg). Oral and intravenous LD50 in mice is 38 and 21 mg/kg, respectively. As mentioned above, the main target organ in all mammals including man is the lung with resulting pulmonary edema and congestion and severe respiratory distress. Necrotic changes are also found in the liver of hamsters and in the kidneys of mice (Dutcher and Boyd, 1979; Boyd and Dutcher, 1981). The time course of endothelial lung tissue damage in mice has been studied (Durham et al., 1985).

5. Carcinogenic effects: No carcinogenicity due to 4-IP has been reported. On the contrary, the speculation has been made that 4-IP might be a possible anticarcinogen in man since "non-small cell" cancers have certain characteristics of Clara or type II cells which react with 4-IP (Falzon et al., 1986).

6. Mutagenic and teratogenic efforts: No such effects have been reported.

Emergency Treatment

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash skin with soap and water. Skin should not be rinsed with organic solvents or scanned with UV light. Avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with copious quantities of running water for at least 15 minutes. Obtain ophthalmological evaluation.

2. Ingestion: Drink plenty of water or milk. Induce vomiting. Refer for gastric lavage.

3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.

4. Refer to physician at once. Consider treatment for pulmonary irritation.

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